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Subjects with higher physical activity levels have more severe focal knee lesions diagnosed with 3 T MRI: analysis of a non-symptomatic cohort of the osteoarthritis initiative

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S U M M A R Y

Purpose: To study the prevalence of focal knee abnormalities using 3 Tesla (T) magnetic resonance (MR) studies in relation to physical activity levels in asymptomatic, middle-aged subjects from the osteoarthritis initiative (OAI).
Material and methods: We analyzed baseline data from 236, 45–55 years old individuals (136 women, 100 men) without knee pain (based on Western Ontario and McMaster University scores) and a body mass index (BMI) of 19–27 kg/m^2. Physical activity levels were determined in all subjects using the Physical Activity Scale for the Elderly (PASE). MR imaging (MRI) at 3 T was performed using coronal intermediate-weighted (IW) 2D fast spin-echo (FSE), sagittal 3D dual-echo in steady state (DESS) and 2D IW fat-suppressed (fs) FSE sequences of the right knee. All images were analyzed by two musculoskeletal radiologists identifying and grading cartilage, meniscal, ligamentous and other knee abnormalities using the whole-organ MR imaging score (WORMS) MRI OA scoring method. Statistical significances between subjects with different activity levels were determined using one-way analysis of variance (ANOVA), chi-square tests and a multi-variate regression model adjusted for gender, age, BMI, Kellgren–Lawrence (KL) score and osteoarthritis (OA) risk factors.
Results: Meniscal lesions were found in 47% of the 236 subjects, cartilage lesions in 74.6%, bone marrow edema pattern (BMEP) in 40.3% and ligament lesions in 17%. Stratification of subjects by physical activity resulted in an increasing incidence of cartilage, meniscus and ligament abnormalities, BMEP and joint effusion according to activity levels (PASE). The severity grade of cartilage lesions was also associated with PASE levels and presence of other knee abnormalities was also significantly associated with cartilage defects.
Conclusion: Asymptomatic middle-aged individuals from the OAI incidence cohort had a high prevalence of knee abnormalities; more physically active individuals had significantly more and more severe knee abnormalities independently of gender, age, BMI, KL score and OA risk factors. These data therefore also suggest that subjects with higher physical activity levels may be at greater risk for cartilage, meniscus and ligament abnormalities, but the analysis of the longitudinal data will show whether these subjects will demonstrate accelerated progress.

Introduction

A public health emphasis on personal fitness with regular physical activity has reduced risk factors for chronic diseases and disabilities. In addition, the individuals who are regularly exercising have physical, psychological and social benefits[1]. The association of physical activity and the risk for developing osteoarthritis (OA), however, is still not well understood and no conclusive data on the impact of physical activity on the onset of OA is available[2]. OA is

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a multi-factorial degenerative joint disease and a leading cause of disability worldwide, with radiographic evidence of OA present in 70% of the population over the age of 65, and nearly 27 million individuals in the US with clinically symptomatic knee OA[3].

OA is characterized by the progressive loss of hyaline articular cartilage, and the development of altered joint congruency, subchondral sclerosis, intra-osseus cyst formation and osteophytes. Magnetic resonance imaging (MRI) has an ever-increasing role in the diagnosis and monitoring of OA[4] with typical imaging characteristics including cartilage defects, meniscal and ligamentous abnormalities, bone marrow edema like lesions as well as subchondral cysts[3,5]. To better understand the natural evolution of OA using MRI the National Institutes of Health (NIH) launched the OA initiative (OAI), a longitudinal, observational multi-center study enrolling 4796 patients. The study has created a public archive of data, biological samples and joint images at four recruitment centers across the United States, focusing primarily on knee OA. In addition to MRI data the OAI provides information on muscle strength, physical activity, pain and function in cohorts of patients with risks for OA (incidence cohort) and evidence of OA (progression cohort). Thus sampling strategy allows a thorough analysis of clinical factors associated with morphological abnormalities of the knee assessed with MRI.

The aim of this study was to study prevalence and grade of focal knee abnormalities using 3 T MR studies in relation to physical activity levels and muscle strength in asymptomatic, middle-aged subjects from the OAI incidence cohort.

Material and methods

Subjects

A subset of 236 subjects (Fig. 1) of the 4796 OAI study subjects, which fulfilled our inclusion criteria, was included in this study. The OAI is an ongoing 4-year, multi-center, longitudinal, prospective observational cohort study, focusing primarily on knee OA. The study protocol, amendments, and informed consent documentation including analysis plans were reviewed and approved by the local institutional review boards. Data used in the preparation of this article were obtained from the OAI database, which is available for public access at http://www.oai.ucsf.edu/. Specific datasets used are baseline clinical datasets 0.2.2 and baseline image dataset 0.E.1. All subjects were recruited from the incidence cohort of the OAI, these subjects were characterized by absence of symptomatic knee OA but risk factors for OA. These risk factors included knee symptoms (pain, aching or stiffness in or around the joints) in the past 12 months but not on most days for at least 1 month. In addition a history of knee surgery and injury as well as a family history of total knee replacement and Heberden nodes are defined as risk factors. Exclusion criteria were rheumatoid arthritis, severe joint space narrowing and contraindications or inability for MRI.

Specific inclusion criteria for the subjects in this project were: (1) age range: 45–55 years, (2) body mass index (BMI) of 19–27 kg/m^2 and (3) Western Ontario and McMaster University (WOMAC) pain score of zero at the time of the MRI. Based on these criteria 4560 subjects from the OAI cohort were excluded as visualized in Fig. 1. These criteria were used to exclude obesity as a risk factor for OA and to focus on younger subjects. Based on these criteria 136 women and 100 men were identified and included in this project.

Questionnaires and clinical examinations

WOMAC

The WOMAC OA index was used to include subjects without knee pain in this study. The WOMAC score is one of the best established scores to assess clinical symptoms of OA, it is a multidimensional health status instrument that quantifies pain, stiffness, physical and emotional function in patients with OA of the knee and hip[6,7].

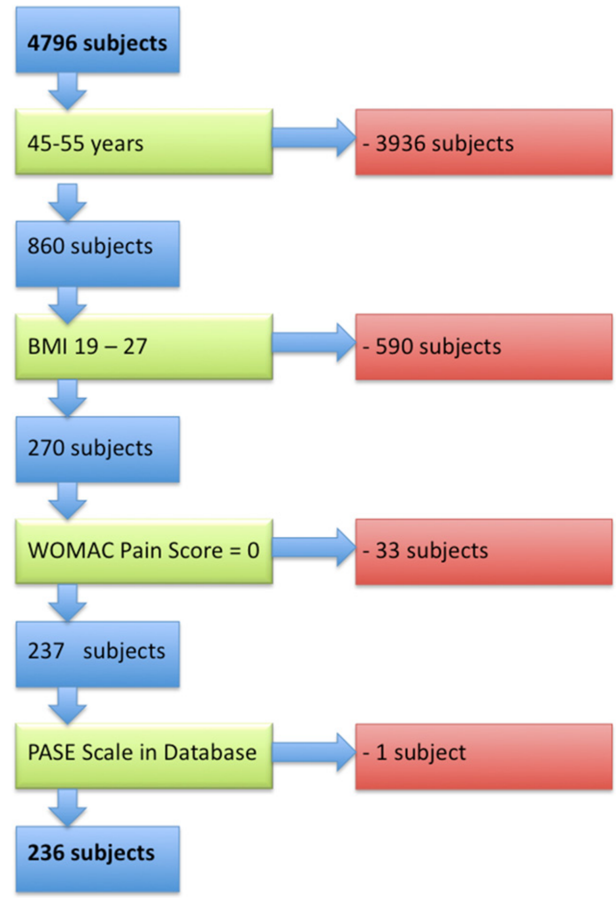

Fig. 1. The diagram illustrates how the subcohort of our study was created. Specific inclusion criteria for the subjects in this study were used were: (i) age range: 45–55 years, (ii) BMI of 19–27 and (iii) WOMAC pain score of zero at the time of the MRI. Based on these criteria 4560 subjects from the OAI cohort were excluded.

Physical Activity Scale for the Elderly (PASE)

Physical activity levels were quantified in all subjects using the PASE, which is an established questionnaire to measure physical activity in older individuals[8]. Washburn *et al.*[8] found the PASE to be a reliable and valid instrument for the assessment of physical activity in epidemiologic studies. The scale range is 0–400 with an average of 160 given in the previous study. The PASE scale has been used in populations with similar age distributions previously[9].

Knee injury and OA outcome score (KOOS)

The KOOS was developed as an extension of the WOMAC OA index with the purpose of evaluating short-term and long-term symptoms and function in subjects with knee injury and OA. The KOOS differentiates five separately scored subscales: pain, other symptoms, function in daily living, function in sport and recreation and knee-related quality of life[10].

Clinical examinations

All subjects completed a 400 m walk, repeated chair stands and isometric muscle strength tests. The time in seconds for a 400 m walk of each subject was measured. The 400-m walk, a modification of the validated and widely used 6-min walk, is a self-paced endurance test that includes standardized encouragement and modifications that increase tolerability in elders and those with physical impairment[11,12]. Walking endurance is a secondary outcome measure recommended by the OA Research Society[13,14] and has been successfully used as an outcome measure in several trials investigating knee OA treatment[15]. The repeated chair stands were calculated as stands per second. The maximum isometric strength of the right knee was obtained in maximum force flexion and extension. Bilateral isometric knee extensor and flexor strength were measured using the Good Strength Isometric Strength Chair (Metitur, Jyvaskyla, Finland)[16,17]. The maximal force produced during isometric contraction was measured in Newton during isometric contractions of the right and left quadriceps and hamstring muscles at a knee angle of 60° from full extension.

Imaging

Bilateral radiographs

Bilateral standing posterior–anterior (PA) "fixed flexion" knee radiographs were obtained. Knee radiographs were obtained in a plexiglass positioning frame (SynaFlexerTM) with 20–30° flexion and 10° internal rotation of bilateral feet. A focus-to-film distance of 72 inches was used. All radiographs were evaluated by two radiologists in consensus and graded using the Kellgren–Lawrence (KL) grading scale[5,18].

MRI

All knee examinations were obtained with four identical 3 T MRI systems (Trio, Siemens, Erlangen, Germany) using a standard knee coil. The following sequences of the right knee were analyzed in this study: (1) coronal intermediate-weighted (IW) 2D fast spin-echo (FSE), (2) sagittal 3D dual-echo in steady state (DESS) with selective water excitation (WE) and (3) sagittal 2D IW fat-suppressed (fs) FSE sequences (FS)[19]. The sequence parameters are presented in Table I.

Table I
OAI knee MRI protocol acquisition parameters

Scan	COR IW 2D TSE	SAG 3D DESS WE	COR T1W 3D FLASH WE	SAG IW 2D TSE FS
Plane	Coronal	Sagittal	Coronal	Sagittal
FS	No	WE	WE	FS
Matrix (phase)	307	307	512	313
Matrix (frequency)	384	384	512	448
No. of slices	35	160	80	37
Field of view (FOV) (mm)	140	140	160	160
Slice thickness/gap (mm/mm)	3/0	0.7/0	1.5/0	3/0
Flip angle (°)	180	25	12	180
Time to echo (TE)/Time to repeat (TR) (ms/ms)	29/3700	4.7/16.3	7.57/20	30/3200
Bandwidth (Hz/pixel)	352	185	130	248
Chemical shift (pixels)	1.3	0	0	0
No. of excitations averaged	1	1	1	1
Echo train length (ETL)	7	1	1	5
Phase encode axis	R/L	A/P	R/L	A/P
Distance factor (%)	0	0	0	0
Phase oversampling	20	0	0	40
Slice oversampling	0	10	0	0
Phase resolution	80	80	100	70
Phase partial Fourier (8/8 = 1)	1	1	1	1
Readout partial Fourier	1	1	1	1
Slice partial Fourier	1	0.75	0.75	1
X-resolution (mm)	0.365	0.365	0.313	0.357
Y-resolution (mm)	0.456	0.456	0.313	0.511

MR image analysis

The whole-organ MR imaging score (WORMS) was used to semi-quantitatively evaluate the images[20–22]. Since only a relatively small number of lesions was expected in the middle-aged, asymptomatic subjects the number of anatomical compartments was reduced from 15 to 6 compartments and included the patella, trochlea, medial and lateral femur, and medial and lateral tibia. Using the semi-quantitative scoring system the following structures were separately evaluated: (1) cartilage, (2) ligaments, (3) menisci, (4) bone marrow edema pattern (BMEP), (5) osteophytes, (6) synovitis/effusion, (7) subarticular cysts, (8) flattening or depression of the articular surfaces, (9) loose bodies and (10) popliteal cysts.

All MR images of the right knee were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ, USA) by two musculoskeletal radiologists separately with 20 and 4 years of experience in musculoskeletal imaging; if scores were not identical consensus readings by both radiologists were performed. During the reading session ambient light was reduced and no time constraints were used.

Cartilage abnormalities were scored using an eight-point scale: 0 = normal thickness and signal; 1 = normal thickness but abnormal signal on fluid sensitive sequences; 2.0 = partial-thickness focal defect < 1 cm in greatest width; 2.5 = full-thickness focal defect < 1 cm in greatest width; 3 = multiple areas of partial-thickness (Grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but <75% of the region; 4 = diffuse (≥75% of the region) partial-thickness loss; 5 = multiple areas of full-thickness loss (Grade 2.5) or a Grade 2.5 lesion wider than 1 cm but <75% of the region; 6 = diffuse (≥75% of the region) full-thickness loss.

Alterations in meniscal morphology were assessed separately in six regions (medial and lateral: anterior, body, posterior) using a four-level scale (0, normal; 1, intra-substance abnormalities; 2, non-displaced tear; 3, displaced or complex tear; 4, complete destruction/maceration). Meniscal extrusion was graded as follows: 0, none; 1, meniscal extrusion of more than 3 mm beyond the tibia plateau.

Subarticular bone marrow abnormalities were defined as poorly marginated areas of increased signal intensity in the normal subchondral and epiphyseal bone marrow on fs fluid sensitive FS. This feature was graded from 0 to 3 based on the extent of regional involvement 0 = none; 1 = <25% of the region; 2 = 25–50% of the region; 3 = >50% of the region. Ligaments and joint effusion were evaluated using a four point scale from 0 to 3 (0 = no lesion, 1 = Grade 1 sprain (signal changes around ligament), 2 = Grade 2 sprain (partial tear), 3 = Grade 3 sprain (complete tear) for ligaments; 0 = normal, 1 = <33% of maximum potential distention, 2 = 33–66% of maximum potential distention, 3 = >66% of maximum potential distention for joint effusion). Based on the MR findings a knee was defined as abnormal if a WORMS value of ≥1 was found.

Cartilage lesions were also graded using the MRI classification described by Recht *et al.*[5,23] based on the arthroscopic Noyes and Stabler[24] scoring system: Grade I lesions were defined as having areas of inhomogeneous signal intensity on fat-saturated IW FS; Grade II lesions, as cartilage defects that involved less than half of the articular cartilage thickness; Grade III lesions, as cartilage defects involving more than half of the cartilage but less than full thickness; and Grade IV lesions, as full-thickness cartilage defects exposing the bone.

For all different knee abnormalities WORMS summation scores were calculated, for the articular cartilage we also calculated the

Recht summation scores, WORMS maximum scores and Recht maximum scores were also created.

Statistical analysis

All statistical processing was performed with JMP software Version 7 (SAS Institute, Cary, NC, USA). Descriptive statistics were obtained and statistical significance for differences of measurements between male and female were determined using one-way analysis of variance (ANOVA) and chi-square tests (likelihood ratio). A multi-variate regression model was used for correlations to correct the data for the impact of age, gender, BMI, KL score and risk factors of the incidence cohort (knee injury or surgery in history, family history of knee replacement and Herbeden's nodes in hands). The level of significance was defined for all calculations as $P < 0.05$.

Reproducibility measurements

Reproducibility of the semi-quantitative assessments of different knee abnormalities using the WORMS score for each compartment was calculated in a sample of 12 OAI image datasets that were each assessed twice by each of the two radiologists. Each subregion was graded using the WORMS score and grades given by each radiologists were compared. The inter- and intra-observer agreement was based on the exact rating of each feature, not just the presence or absence of each feature and expressed as intra-class correlation coefficients (ICC) by treating the data as continuous variables[22].

Results

Subject characteristics

Questionnaires, physical examination and risk factors

Table II lists subject characteristics combined and separated for females and males including risk factors in the incidence cohort, age, BMI, PASE values, KOOS-scores, 400 m walk, repeated chair stand and muscle strength. Of the 236 subjects, 57.6% were women. The mean age was 50.59 ± 2.95 years and the mean BMI was 23.85 ± 2.01. Previous knee injury in the medical history was the most common risk factor for OA in our cohort (25%) followed by Herberden's nodes at the hands (15.68%), family history of knee replacement (12.71%) and knee surgery in the medical history (10.17%). Knee surgery was more common in men, whereas the Herberden's nodes were more frequently found in women. While there were no gender related differences concerning age, KL scores, PASE values, KOOS scores, time required for 400 m walk and repeated chair stands, women had significantly lower BMI and muscle strength.

Radiographic evaluation

Radiographs were graded as normal in most of the subjects (KL score = 0, 69.07%, 163/236). KL scores of 1 were found in 24.6% (58/236) of the subjects and KL scores of 2, 3 and 4 in 2.54% (6/236), 3.39% (8/236) and 0.42% (1/236) of all subjects.

Table II
Patient characteristics, clinical history, physical examinations and imaging findings combined and separated for females and males in 236 subjects. A WORMS was used to semi-quantitatively evaluate the images. Cartilage abnormalities were recorded using a WORMS-based threshold of 1 and 2, i.e., including and excluding Grade 1 abnormalities (cartilage signal change). Statistical significance was determined using a chi-square test by Pearson and ANOVA test

	All		Male		Female		Statistical analysis (*P*)
	All (mean)		Male (mean)		Female (mean)		ANOVA
Age	50.59 ± 2.95		50.52 ± 3.03		50.65 ± 2.9		0.7446
BMI	23.85 ± 2.01		24.59 ± 1.59		23.31 ± 2.11		0.0001*
PASE	193.87 ± 80.21		202.49 ± 79.49		187.53 ± 80.76		0.1573
KOOS score	93.25 ± 10.33		92.12 ± 10.59		94.11 ± 10.10		0.1602
400 m walk (sec)	271.80 ± 30.17		271.37 ± 33.34		272.16 ± 27.36		0.8594
Repeated chair stand (stands/s)	0.61 ± 0.15		0.61 ± 0.15		0.60 ± 0.15		0.662
Right flexion max force	163.86 ± 67.87		191.831 ± 78.66		141.43 ± 47.40		0.0001*
Right extension max force	396.92 ± 116.32		462.09 ± 114.92		344.66 ± 87.92		0.0001*
	Number/236	Percentage	Number/100	Percentage	Number/136	Percentage	Chi-Sq (Pearson)
Risk factors incidence cohort							
Knee injury in history	59	25.00	31	31.00	28	20.59	0.068
Knee surgery in history	24	10.17	17	17.00	7	5.15	0.0029*
Family history (knee replacement)	30	12.71	15	15.00	15	11.03	0.3655
Heberden's nodes in hands	37	15.68	6	6.00	31	22.79	0.0005*
KL score							0.7771
KL 0 (numbers)	163	69.07	69	69.00	94	69.12	
KL 1 (numbers)	58	24.58	24	24.00	34	25.00	
KL 2 (numbers)	6	2.54	2	2.00	4	2.94	
KL 3 (numbers)	8	3.39	4	4.00	4	2.94	
KL 4 (numbers)	1	0.42	1	1.00	0	0.00	
Lesions							
Meniscus	111	47.0	54	54.0	57	41.9	0.066
Ligaments	40	17.0	23	23.0	17	12.5	0.0336*
Cartilage all lesions	176	74.6	72	72.0	104	76.5	0.4357
Cartilage lesions WORMS > 1	138	58.5	54	54.0	84	61.8	0.2316
Bone marrow edema	95	40.3	44	44.0	51	37.5	0.3143
Depression of articular surface	2	0.9	2	2.0	0	0.0	0.0977
Subarticular cysts	18	7.6	9	9.0	9	6.6	0.4957
Osteophytes	89	37.7	37	37.0	52	38.2	0.8466
Joint effusion	61	25.9	29	29.0	32	23.5	0.3428
Loose bodies	8	3.4	5	5.0	3	2.2	0.2412
Popliteal cysts	31	25.8	18	30.0	13	21.7	0.3295

* Statistical significant.

Prevalence of focal knee MR abnormalities

Tables II and III summarize knee abnormalities found in all subjects. A high prevalence of both, cartilage and meniscal lesions was found in the study subjects. Meniscal lesions were found in 111/236 (47%) subjects and were more frequently found in men (54/100; 54%) than in women (57/136; 41.9%, $P = 0.066$). Subjects with meniscal lesions frequently had abnormalities in more than one region of the meniscus; 219 abnormalities were diagnosed in all six compartments. Lesions at the medial meniscus were more common than at the lateral meniscus (166/219; 75.8% vs 53/219; 24.2%) The posterior horn of the medial meniscus was most frequently involved (97/219; 44.29%) followed by the body of the medial meniscus (57/219; 26.03%). The prevalence of intra-substance signal abnormalities was highest (94/219; 42.92%, WORMS 1), followed by non-displaced tears (70/219; 31.96% WORMS 2) with 57/219 (26.03%) horizontal tears. Mild meniscal abnormalities such as WORMS 1 lesions were more common in women (53.85% vs 33.04%) while more severe lesions were more commonly found in men (WORMS 4 in 20% vs 8.65%).

One hundred and seventy-six of 236 subjects (74.6%) had cartilage abnormalities, which were more prevalent in women than in men (76.5% vs 72%). Subjects frequently had abnormalities in more than one region of the cartilage with 370 abnormalities were recorded in all six compartments. A high percentage of cartilage abnormalities was found at the patella (149/370; 40.27%) followed by the trochlea

Table III
Anatomical distribution of meniscus, ligament and cartilage abnormalities and distribution according to gradings with WORMS and Recht scores

Lesions	All		Male		Female	
	Number	Percentage	Number	Percentage	Number	Percentage
Meniscus lesions in subjects	111/236	47.0	54/100	54.0	57/136	41.9
Meniscus lesions total	219		115		104	
Medial anterior	12/219	5.48	10/115	8.70	2/104	1.92
Medial body	57/219	26.03	32/115	27.83	25/104	24.04
Medial posterior	97/219	44.29	51/115	44.35	46/104	44.23
Lateral anterior	20/219	9.13	8/115	6.96	12/104	11.54
Lateral body	10/219	4.57	5/115	4.35	5/104	4.81
Lateral posterior	23/219	10.50	9/115	7.83	14/104	13.46
WORMS						
1 = intra-substance abnormalities	94/219	42.92	38/115	33.04	56/104	53.85
2 = non-displaced tear	70/219	31.96	39/115	33.91	31/104	29.81
-horizontal tear	57/219	26.03	29/115	25.22	28/104	26.92
3 = displaced or complex tear	21/219	9.59	15/115	13.04	6/104	5.77
4 = maceration of the meniscus	34/219	15.53	23/115	20.00	9/104	8.65
-extrusion	8/219	3.65	5/115	4.35	3/104	2.88
Ligament lesions in subjects	40/236	16.95	23/100	23.00	17/136	12.50
Ligament lesions total	48		30		18	
ACL	17/48	35.42	9/30	30.00	8/18	44.44
PCL	6/48	12.50	3/30	10.00	3/18	16.67
MCL	7/48	14.58	5/30	16.67	2/18	11.11
LCL	5/48	10.42	4/30	13.33	1/18	5.56
Pobliteus	0/48	0.00	0/30	0.00	0/18	0.00
Patellar ligament	13/48	27.08	9/30	30.00	4/18	22.22
WORMS						
Grade 1 sprain	13/48	27.08	8/30	26.67	5/18	27.78
Grade 2 sprain	32/48	66.67	19/30	63.33	13/18	72.22
Grade 3 sprain	3/48	6.25	3/30	10.00	0/18	0.00
Cartilage lesions in subjects	176/236	74.58	72/100	72.00	104/136	76.47
Cartilage lesions total	370		166		204	
Patella	149/370	40.27	58/166	34.94	91/166	44.61
Trochlea	62/370	16.76	25/166	15.06	37/166	18.14
MFC	56/370	15.14	30/166	18.07	26/166	12.75
LFC	30/370	8.11	12/166	7.23	18/166	8.82
MT	25/370	6.76	18/166	10.84	7/166	3.43
LT	48/370	12.97	23/166	13.86	25/166	12.25
WORMS 1	119/370	32.16	58/166	34.94	61/166	29.90
WORMS 2	66/370	17.84	31/166	18.67	35/166	17.16
WORMS 2.5	20/370	5.41	12/166	7.23	8/166	3.92
WORMS 3	106/370	28.65	35/166	21.08	71/166	34.80
WORMS 4	9/370	2.43	2/166	1.20	7/166	3.43
WORMS 5	41/370	11.08	26/166	15.66	15/166	7.35
WORMS 6	9/370	2.43	2/166	1.20	7/166	3.43
Recht 1	119/370	32.16	58/166	34.94	61/166	29.90
Recht 2	122/370	32.97	50/166	30.12	72/166	35.29
Recht 3	59/370	15.95	18/166	10.84	41/166	20.10
Recht 4	70/370	18.92	40/166	24.10	30/166	14.71

(62/370; 16.76%) and the medial femur condyle (MFC) (56/370, 15.14%). Signal abnormalities of the cartilage (WORMS 1, Recht 1) were most commonly found (119/370; 32.16%) followed by Grade 3 WORMS lesions (106/370; 28.65%). Similar results were found using the Recht score, where the percentage of Recht 2 lesions was highest (32.97%; 122/370). Full-thickness defects (WORMS 2.5, 5, 6 and Recht 4) were found in a high percentage (18.92%; 70/370) and were more frequent in men than in women (40/166; 24% vs 30.166; 14.71%).

Ligamentous abnormalities were found in 40/236 (17%) subjects and were more prevalent in men than in women (23/100; 23% vs 17/136; 12.5%), were frequently present in more than one ligament. ACL lesions were most common (17/48; 35.4%) followed by lesions of the patellar ligament (13/48; 27.08%). Grade 2 sprains (partial tear) were most frequently diagnosed (32/48; 66.67%).

Reproducibility of clinical readings

The ICC for inter-observer agreement ICC was 0.84; the ICC for the intra-observer agreement was 0.86 and 0.89 respectively and indicated good reproducibility for the scoring of knee abnormalities.

Physical activity in relation to morphological knee abnormalities and patient characteristics

Based on their physical activity level (PASE from 27 to 378) subjects were divided into three groups with the same PASE range of 117 and were defined as low activity group with PASE values of 27–144 ($n = 68$), as medium activity group with PASE values of 145–261 ($n = 122$) and as a high activity group subjects with PASE values of 262–378 ($n = 46$) (Tables IV and V).

Subjects with higher PASE scales had higher KL scores ($P < 0.0003$) in the chi-square test. Because of the high correlation with the radiographic KL score the multi-variate regression models were used to assess the impact of physical activity on the different MRI knee abnormalities independent.

The subjects in the three PASE groups had no statistical difference in KOOS-score, repeated chair stands or muscle strength (flexion/extension), however the time for the 400 m walk was significantly decreasing with increasing PASE scale ($P = 0.0011$*).

Prevalence of knee abnormalities was significantly higher in the medium and high PASE scale groups (Fig. 2) for cartilage ($P = 0.0004$), meniscus ($P = 0.0052$), ligament abnormalities ($P = 0.0243$), BMEP (0.0251) and joint effusion ($P < 0.0001$) compared to the low PASE scale group.

Prevalence of cartilage lesions increased with the PASE level, from 60.29% (41/68) in the low PASE group to 75.41% (92/122) in the medium PASE group and 93.48% (43/46) in the high PASE group ($P = 0.0004$). In addition lesions diagnosed in the more active subjects were more severe shown by increasing WORMS and Recht maximum and summation scores ($P < 0.05$), as shown in Table IV with better correlation for WORMS score.

Prevalence of cartilage defects in relation to clinical data and other knee abnormalities diagnosed with MRI

Subjects were divided into a group with and without cartilage lesions and differences in clinical data and other knee abnormalities diagnosed with MRI were analyzed in these subgroups as outlined in Table VI. In 25.4% (60/236) subjects no cartilage lesions

Table IV

Patient characteristics including WORMS and Recht scores separating subjects according to their activity levels (PASE from 27 to 378) into three groups with the same PASE range of 117. They were defined as low activity group with PASE values of 27–144 ($n = 68$), as medium activity group with PASE values of 145–261 ($n = 122$) and as a high activity group subjects with PASE values of 262–378 ($n = 46$). MRI findings and physical examinations are listed. Statistical significance was determined by a multi-variate regression model, *P*-values reflect a test for trend of the dependent variable by the 3-level ordinal PASE variable adjusted for gender, age, BMI, KL score and OA risk factor

	Low PASE scale (27–144)		Middle PASE scale (145–261)		High PASE scale (262–378)		*P*-values for PASE categories
	Number	Percentage	Number	Percentage	Number	Percentage	Multi-regression analysis*
Range PASE per group	117		117		117		
Number of subjects	68/236		122/236		46/236		
Lesions							
Cartilage	41	60.29	92	75.41	43	93.48	0.0004*
Meniscus	21	30.88	60	49.18	30	65.22	0.0052*
Ligaments	7	10.29	19	15.57	14	30.43	0.0243*
Bone marrow edema	19	27.94	51	41.80	25	54.35	0.0251*
Depression of articular surface	0	0.00	1	0.82	1	2.17	0.9999
Subarticular cysts	1	1.47	12	9.84	4	8.70	0.3312
Osteophytes	17	25.00	52	42.62	20	43.48	0.1321
Joint effusion	3	4.41	36	29.51	22	47.83	<0.0001*
Loose bodies	3	4.41	3	2.46	2	4.35	0.0991*
Popliteal cysts	16	23.53	35	28.69	11	23.91	0.981
	Mean ± SD		Mean ± SD		Mean ± SD		*P*-values for PASE categories
Cartilage scores (mean)							
WORMS summation score	2.18 ± 2.91		3.89 ± 4.01		6.33 ± 6.02		0.0003*
Recht summation score	2.0 ± 2.74		3.53 ± 3.42		5.41 ± 4.78		0.0004*
WORMS maximum score	1.43 ± 1.52		2.18 ± 1.74		2.71 ± 1.88		0.0056*
Recht maximum score	1.27 ± 1.30		1.98 ± 1.49		2.26 ± 1.39		0.0082*
Clinical parameters							
KOOS score	94.79 ± 10.53		93.05 ± 10.39		91.63 ± 9.83		0.6387
400 m walk (sec)	280.89 ± 31.17		271.75 ± 31.11		261.55 ± 23.56		0.0011*
Repeated chair stand (stands/s)	0.59 ± 0.15		0.61 ± 0.14		0.62 ± 0.18		0.0945
Right flexion max force	169.36 ± 70.17		166.12 ± 72.79		152.36 ± 51.89		0.3812
Right extension max force	381.4 ± 138.4		397.17 ± 113.16		414.28 ± 93.92		0.0401*

* Correction for age, gender and BMI, KL score, knee injury or knee surgery in history, family history of knee replacement and Herbeden's nodes in hands.

Table V
Table where the subjects were divided by all six compartments and the specific WORMS grades for cartilage and meniscal lesions and Recht scores for cartilage lesions (Additional information to Table IV). Like in Table IV, the subjects were separated according to their activity levels (PASE from 27 to 378) into three groups with the same PASE range of 117

	Low PASE scale (27–144)		Middle PASE scale (145–261)		High PASE scale (262–378)		*P*-values for PASE categories
	Number	Percentage	Number	Percentage	Number	Percentage	Multi-regression analysis*
Range PASE per group	117		117		117		
Number of subjects	68/236		122/236		46/236		
Subjects × compartments (236 × 6)	408/1416		732/1416		276/1416		
Lesions							
Subjects with cartilage lesions	*41/68*	*60.29*	*92/122*	*75.41*	*43/46*	*93.48*	0.0004*
Divided by WORMS scores							
Cartilage WORMS 1	23/408	5.64	53/732	7.24	43/276	15.58	
Cartilage WORMS 2	18/408	4.41	38/732	5.19	10/276	3.62	
Cartilage WORMS 2.5	1/408	0.25	11/732	1.50	8/276	2.90	
Cartilage WORMS 3	19/408	4.66	58/732	7.92	29/276	10.51	
Cartilage WORMS 4	1/408	0.25	5/732	0.68	3/276	1.09	
Cartilage WORMS 5	5/408	1.23	19/732	2.60	17/276	6.16	
Cartilage WORMS 6	0/408	0	5/732	0.68	4/276	1.45	
Divided by Recht scores							
Cartilage Recht 1	23/408	6	53/732	3.74	43/276	15.58	
Cartilage Recht 2	27/408	7	63/732	8.61	32/276	11.59	
Cartilage Recht 3	10/408	2	38/732	5.19	10/276	3.62	
Cartilage Recht 4	7/408	2	35/732	4.78	29/276	10.51	
Subjects with meniscus lesions	*21/68*	*30.88*	*60/122*	*49.18*	*30/46*	*65.22*	0.0052*
Divided by WORMS scores							
Meniscus WORMS 1	14/408	3.43	45/732	6.15	35/276	12.68	
Meniscus WORMS 2	8/408	1.96	44/732	6.01	18/276	6.52	
Meniscus WORMS 3	6/408	1.47	10/732	1.37	5/276	1.81	
Meniscus WORMS 4	0/408	0	26/732	3.55	8/276	2.90	

* Correction for age, gender and BMI, KL score, knee injury or knee surgery in history, family history of knee replacement and Herbeden's nodes in hands.

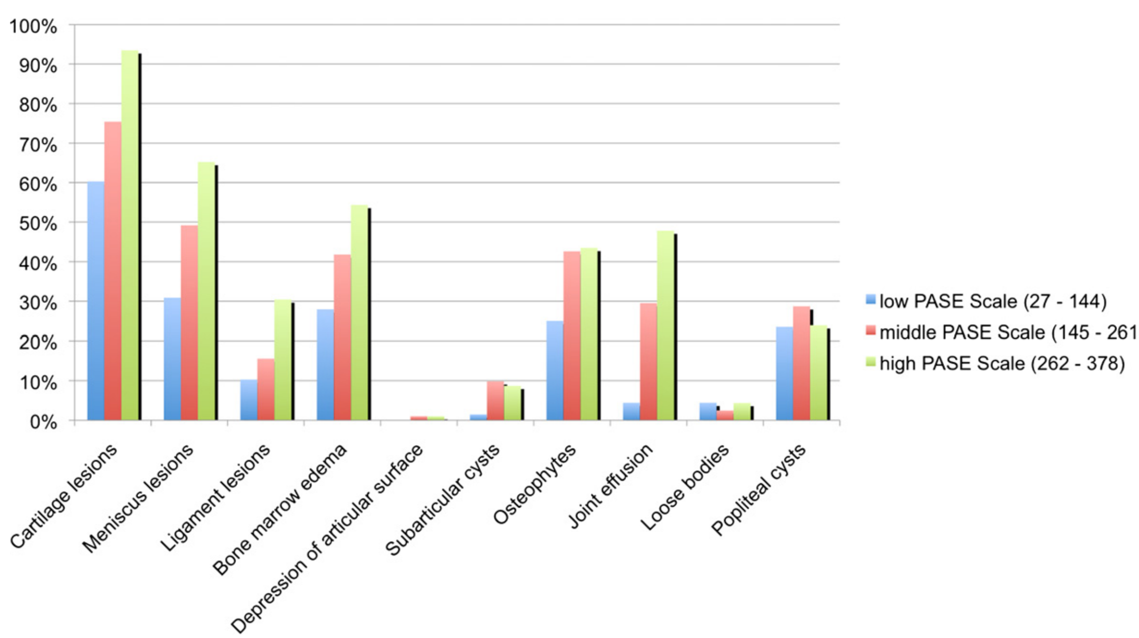

Fig. 2. Prevalence of knee abnormalities differentiating subjects according to their activity level divided into three PASE scale groups. Results are given as percentages. Prevalence of knee abnormalities was significantly higher in the medium and high PASE scale groups for cartilage ($P = 0.0004$), meniscus ($P = 0.0052$), ligaments ($P = 0.0243$), BMEP (0.0251) and joint effusion ($P < 0.0001$) compared to the low PASE scale group. MRI findings and physical examinations are listed. Statistical significance was determined by a multi-variate regression model, *P*-values reflect a test for trend of the dependent variable by the three-level ordinal PASE variable adjusted for gender, age, BMI, KL score and OA risk factors.

Table VI
Subjects separated according to presence and absence of cartilage lesions (WORMS 1–6 vs WORMS 0). MRI findings, and physical examinations are listed. Statistical significance was determined by a multi-variate regression model, *P*-values are for cartilage WORMS categories (ordinal variable) as a predictor adjusted for gender, age, BMI, KL score and OA risk factors

	Cartilage WORMS				
	WORMS 0		WORMS 1–6		*P*-values for cartilage categories
	Number	Percentage	Number	Percentage	Multi-regression analysis*
Number of subjects	60/236	25.42	176/236	74.58	
Lesions					
Meniscus	17/60	28.3	94/176	53.41	0.0227*
Ligaments	2/60	3.33	38/176	21.59	0.0016*
Bone marrow edema	1/60	1.67	94/176	53.41	<0.0001*
Depression of articular surface	0	0	2/176	1.14	1
Subarticular cysts	0	0	18/176	10.30	0.0131*
Osteophytes	5/60	8.33	84/176	47.73	0.0037*
Joint effusion	1/60	6.00	60/176	34.09	<0.0001*
Loose bodies	0	0	8/176	4.55	0.1011
Popliteal cysts	17/60	28.33	45/176	25.6	0.8699
	Mean ± SD		Mean ± SD		*P*-values for cartilage categories
Clinical parameters					
PASE-scale	163.78 ± 63.55		204.13 ± 82.84		0.0023*
KOOS score	95.7 ± 7.02		92.4 ± 11.15		0.1895
400 m walk (s)	280.5 ± 31.32		268.92 ± 29.33		0.0161*
Repeated chair stand (stands/s)	0.62 ± 0.15		0.60 ± 0.15		0.4614
Right flexion max force	170.93 ± 72.13		161.52 ± 66.52		0.4179
Right extension max force	401.77 ± 136.3		395.32 ± 109.46		0.852

* Correction for age, gender and BMI, KL score, knee injury or knee surgery in history, family history of knee replacement and Herbeden's nodes in hands.

were found (WORMS 0) while 74.6% (176/236) had cartilage abnormalities (WORMS 1–6).

Subjects with cartilage lesions had significantly higher PASE scales (204.13 ± 82.84 vs 163.78 ± 63.55; $P = 0.0023$), and a decreased time for the 400 m walk (268.92 ± 29.33 vs 280.5 ± 31.32; $P = 0.02$). Subjects with cartilage lesions (Grade > 3) did not show a correlation with PASE ($P = 0.24$). The KOOS score, the muscle strengths and the time for repeated chair stands decreased but not significant.

A significantly higher incidence of meniscus and ligament lesions, BMEP, subarticular cysts, osteophytes and joint effusions was found in the cartilage lesion group ($P < 0.0001$–0.02) (Table VI, Fig. 3).

Discussion

Middle-aged, non-symptomatic individuals from the OAI incidence cohort had a very high prevalence of knee abnormalities such as cartilage, meniscus, and ligament lesions. The prevalence of the knee abnormalities increased with the level of physical activity, also cartilage defects, diagnosed in active subjects, were more severe. When dividing the subjects into a group with and without cartilage abnormalities, a significantly higher number of meniscus and ligament lesions, BMEP, subarticular cysts, osteophytes and joint effusion were found to be associated with cartilage lesions.

High numbers of meniscus lesions in asymptomatic subjects were also found by other investigators[25–27]: Zanetti *et al.*[25] found

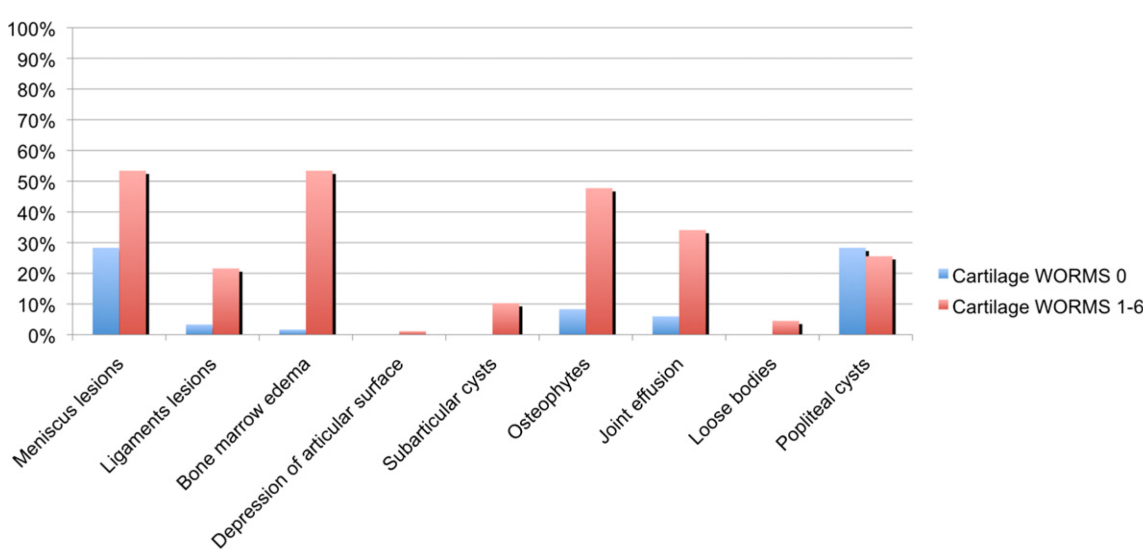

Fig. 3. Subjects separated according to presence and absence of cartilage lesions (WORMS 1–6 vs WORMS 0). Results are given as percentages. A significantly higher incidence of meniscus and ligament lesions, BMEP, subarticular cysts, osteophytes and joint effusions was found in the cartilage lesion group ($P < 0.0001$–0.02). Statistical significance was determined by a multi-variate regression model adjusted for gender, age, BMI, KL score and OA risk factors.

meniscal tears in 36/100 asymptomatic knees (mean age, 42.7 years, age range 18–73 years). The prevalence in our study was even higher with 47% of our subjects demonstrating meniscal lesions, but we also included Grade 1 lesions, in contrast to their study. Our mean age was higher (50.59 ± 2.95 years with an age range from 45–55 years) which may in part explain the differences in prevalence. In another previous study by Englund *et al.*[26] the authors described the prevalence of meniscal abnormalities from 19% among women who were 50–59 years old to 56% among men who where 70–90 years old (mean age 62.3 years, age range 16.6–55.6). We also found a higher prevalence of meniscal abnormalities in male (54%; 54/100) compared to female subjects (42.9%; 57/136). They did not include intra-substance abnormalities, which also may explain the higher prevalence of meniscal abnormalities in our study.

Beattie *et al.*[27] reported a relatively low prevalence of cartilage lesions of only 11%, (5/44). The trochea, medial femur and patella were the most affected regions. They also included areas of signal change in the cartilage abnormalities and images were assessed with relative low field strength a 1.0 T. Zanetti *et al.*[25] reported a prevalence of cartilage lesions of 25% (25/100) in the asymptomatic knees. They also included cartilage signal changes and used a 1.0 T scanner. In contrast we found cartilage lesions in 74.6% (176/236) of subjects in our OAI subcohort. Similar to the previous mentioned studies most cartilage lesions were found in certain anatomic subregions like the patella, trochlea and MFC. We found mostly signal abnormalities followed by cartilage thinning. Also we used higher field strengths (3 T), which may also in part explain the higher prevalence of cartilage abnormalities. A number of *in vitro* studies were performed comparing visualization of cartilage, ligaments and menisci at 1.5 and 3 T[28–32]. Wong *et al.* demonstrated an increase in sensitivity and diagnostic performance observed at 3 T for cartilage lesion detection of the knee[31] and Masi *et al.* demonstrated improved diagnostic performance at 3 T vs 1.5 T MRI for cartilage lesions in a porcine model.

The relationship of physical activity and the evolution of OA is limited and unclear as very few investigations have evaluated the natural history of OA in physical active individuals[33–40]. Some studies have reported that physical activity is associated with risk for knee OA[34,36,37] while other studies have shown that physical activity may have no effect[33,35,38] or even prevent knee OA[39,40]. A number of studies examined OA risk factors in relation to quantitative and qualitative cartilage loss determined with MRI[41–45]. However, there is a paucity of data analyzing focal cartilage abnormalities in relation to physical activity using MRI.

We focused on younger subjects from within the OAI as these could potentially best benefit from preventive intervention. While the asymptomatic, subjects in our cohort already had a high prevalence of knee abnormalities, the physically active individuals showed significantly higher numbers and grades of cartilage, meniscus and ligament abnormalities as well as BMEP and joint effusion compared with more sedentary subjects, even after adjustment for KL scores, age, gender, BMI and OA risk factors. Previous studies showed similar results in smaller populations and younger subjects with higher physical activity levels. Recently Stahl *et al.* examined 10 marathon runners and 12 physically active asymptomatic subjects and found a high prevalence of cartilage abnormalities in the marathon runners (60%) and active controls (50%)[21].

Some investigators[39,46] examined individuals in different age groups and examined the influence of age on the risk for developing knee OA in physically active subjects. McAlindon examined the level of physical activity and the risk of radiographic and symptomatic knee OA in an elderly population of the Framingham Study. They found, that vigorous physical activity is an important risk factor for the development of knee OA in the elderly[46]. In contrast to these results, a lower prevalence of OA was reported in middle-aged (48–60 years) physically active teachers as compared with controls[39]. These investigators based their diagnosis on radiographs, which unfortunately show already advanced disease stages, which may limit disease preventive measures.

A small number of studies[47–50] used MRI to examine the relationship between knee abnormalities and physical activity. Stahl *et al.*[47] showed in a small cohort that physically active subjects had a higher prevalence of focal cartilage abnormalities. Nine of 13 subjects in the active control group and two out of seven subjects in the sedentary control group had abnormal cartilage and/or bone marrow findings. In some studies the most frequent findings in physically active subjects were abnormalities in meniscal signal intensity or tears (prevalence 13%–50%), BMEP (up to 41%) or joint effusion (up to 35%)[48–50]. Prevalence of cartilage lesions was examined in a study of 20 basketball players with MRIs of both knees and reported to be 47.5%[50] with the majority at the patella (35% of the cases) and the trochlea (25%). Major *et al.* performed a study in 17 varsity basketball players[49] and found abnormal signal intensity at the patellar and trochlear cartilage in eight (24%) of the 34 knees and focal cartilage lesions in six (18%) knees. These studies strongly illustrated the association of high physical activity levels and increased cartilage lesions.

There are limitations in this study. We used a very sensitive threshold for defining "abnormality" such as cartilage and meniscal findings of isolated signal elevation (WORMS Grade I). This is a point of controversy within the research community as it is not clear if these MRI findings have any clinical or biological relevance or if they are prognostic of further tissue degeneration. There is a paucity of data concerning the prognostic significance. We strongly feel, however, that it is required to use MRI to diagnose the earliest pathological findings and Grade 1 lesions would be among the first lesions to diagnose as abnormal cartilage. Subjects with cartilage lesions Grade > 3 did not show a correlation with PASE. The changes might be so severe, that these individuals due to a limited physical activity. As OA progresses physical activity levels will decrease, this, however, will be a very slow process evolving over years and there may be a plateau regarding physical activity for Grade > 3 lesions. The population selected for this study has relatively mild lesions (about 16% $>$ Grade 3) and very limited clinical findings at baseline. To solve this question we will need longitudinal data to show whether these subjects will demonstrate accelerated progress.

Another limitation is the possibility of further knee injuries in our subjects. Participants who are physically active now are also more likely to have had injuries in the past and to have continued to be active after the injury, causing more accelerated joint damage, which may be a potentially confounding factor. Detailed data about injury and associated activity modulation were not acquired, but if participants with prior injury had pain and reduced activity so as to eliminate pain, this would act to attenuate the association of physical activity with lesions. Reproducible data on modulation of activity are not available, but beyond the scope of the observational multi-center study. Future intervention studies are required to address this issue. In prestudies we examined the impact of the OA risk factors like previous knee injury. For example they had significantly higher PASE scales (186.29 ± 79.19 vs 217.98 ± 80.02; $P = 0.009$) and more and higher graded cartilage lesions measured in the WORMS summation score (3.53 ± 3.87 vs 4.92 ± 5.80; $P = 0.039$). That was the reason why we used a multi-variate regression model for correlations to correct the data for the impact of age, gender, BMI, KL score and risk factors of the incidence cohort (knee injury or surgery in history, family history of knee replacement and Herbeden's nodes in hands).

In conclusion our study showed that middle-aged, non-symptomatic individuals from the incidence cohort of the OAI had a high prevalence of knee abnormalities including cartilage, meniscus and ligament lesions; more physically active individuals had significantly more and more severe knee abnormalities after adjusting for gender, age, BMI, KL scores and OA risk factors. Also subjects with cartilage lesions had significantly more additional knee abnormalities. These results demonstrate that there is a high association between the prevalence and grade of different knee abnormalities and physical activity levels as measured with the PASE scale. These data therefore also suggest that subjects with higher physical activity levels may be at greater risk for cartilage, meniscus and ligament abnormalities but the analysis of the longitudinal data will show whether these subjects will demonstrate accelerated progress.

Conflict of interest

No conflict of interest for any authors (Christoph Stehling, Nancy E. Lane, Michael C. Nevitt, John Lynch, Charles E. McCulloch, Thomas M. Link).

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